UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

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OFFICE OF
PREVENTION, PESTICIDES,
AND TOXIC SUBSTANCES

OPP OFFICIAL RECORD
HEALTH EFFECTS DIVISION
SCIENTIFIC DATA REVIEWS
EPA SERIES 361

**MEMORANDUM**

**Date:** 6-October-2009

**Subject:** **Spirodiclofen.** Human-Health Risk Assessment Associated with the Section 3 Registration for Application to Avocado, Black Sapote, Canistel, Mamey Sapote, Mango, Papaya, Sapodilla, and Star Apple.

| | |
|---|---|
| **PC Code:** 124871 | **DP Barcode:** D361071 |
| **Decision No.:** 404221 | **Registration No.:** 264-831 |
| **Petition No.:** 8F7500 | **Regulatory Action:** Section 3 |
| **Risk Assessment Type:** Single Chemical Aggregate | **Case No.:** none |
| **TXR No.:** not applicable | **CAS No.:** 148477-71-8 |
| **MRID Nos:** none | **40 CFR:** 180.608 |

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The Office of Pesticide Programs (OPP) HED assesses the risks posed to humans from exposure to pesticide chemicals. OPP's RD has asked HED to evaluate hazard and exposure data and conduct dietary, occupational, residential and aggregate exposure assessments, as needed, to estimate the risk to human health that will result from all registered/proposed uses for spirodiclofen (3-(2,4-dichlorophenyl)-2-oxo-1-oxaspiro[4,5]dec-3-en-4-yl 2,2-dimethylbutanoate). A summary of the findings and an assessment of human risk are provided in this document. The toxicology review was provided by Rob Mitkus (RABI); the residue chemistry review, dietary exposure analysis, and risk assessment were provided by Tom Bloem (RABI), the occupational/residential exposure (ORE) assessment was provided by Lata Venkateshwara (RABI), and the drinking water assessment was provided by Larry Lui and Faruque Khan of the Environmental Fate and Effects Division (EFED).

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## 1.0 Executive Summary

***Background:*** Spirodiclofen is a tetronic acid with acaricidal action (group 23). It acts by interfering with mite development and controls such pests as *Panonychus* spp., *Phyllocoptruta* spp., *Brevipalpus* spp., and *Aculus* and *Tetranychus* species. The petitioner stated that spirodiclofen is active by contact to mite eggs, all nymphal stages, and adult females (adult males are not affected). Spirodiclofen is currently registered for application to citrus fruit, grape, pome fruit, stone fruit, tree nuts, and hops with tolerances for residues of spirodiclofen *per se* of 0.10-30 ppm; milk and ruminant meat, meat byproducts, and fat tolerances for the combined residues of spirodiclofen and BAJ 2510 are also established (0.02-0.1 ppm; see attachment 1 for structures).

Bayer CropScience (Research Triangle Park, NC) proposed a Section 3 registration for application of Envidor® 2 SC Miticide (suspension-concentrate; 2 lbs ai/gallon; EPA Reg. No. 264-831) to avocado, black sapote, canistel, mamey sapote, mango, papaya, sapodilla, and star apple (1 x 0.31 lb ai/acre; preharvest interval (PHI) = 2 days; restricted entry interval (REI) = 12 hours). In conjunction with the request, the petitioner proposed the establishment of 1.3 ppm tolerances for residues of spirodiclofen *per se* in/on the proposed crops.

***Hazard Characterization:*** Spirodiclofen has a low acute toxicity *via* the oral, dermal, and inhalation routes. It is not an eye or dermal irritant. However, it is a potential skin sensitizer. Following oral administration, spirodiclofen is rapidly absorbed, metabolized, and excreted *via* urine and feces. A rat whole body autoradiography study showed no accumulation in any specific organs or tissues following oral administration. Evidence of developmental toxicity was not observed in the rabbit developmental study. The rat developmental study resulted in an increased incidence of slight dilatation of the renal pelvis (1000 mg/kg/day; highest dose tested (HDT)) at a dose which did not cause maternal toxicity. In the two-generation reproductive toxicity study, developmental effects were observed in $F_1$ males (i.e., delayed sexual maturation, decreased testicular spermatid and epididymal sperm counts (oligospermia); and atrophy of the testes, epididymides, prostate, and seminal vesicles) and $F_1$ females (i.e., increased severity of ovarian luteal cell vacuolation/degeneration) but at a higher dose (1750 ppm) than the systemic effects seen for parents and offspring (350 ppm). Spirodiclofen did not show any evidence of neurotoxicity in the acute and subchronic neurotoxicity studies. In a developmental neurotoxicity study (DNT), a decrease in retention was observed in the memory phase of the water maze for postnatal day (PND) 60 females at all doses. In this DNT study, the morphometric measurements were not performed at the low- and mid-dose; therefore, the registrant conducted a new study using identical experimental conditions as the previous study. The results of the new study demonstrated no treatment related maternal or offspring toxicity at the highest dose tested. Therefore, it can be concluded that spirodiclofen is unlikely to be a neurotoxic or developmentally-neurotoxic compound.

Chronic toxicity and carcinogenicity studies showed increased incidence of uterine adenocarcinoma in female rats, Leydig cell adenoma in male rats, and liver tumors in mice. The HED Cancer Assessment Review Committee (CARC) classified spirodiclofen as "likely to be carcinogenic to humans" by the oral route based on evidence of testes Leydig cell adenomas in male rats, uterine adenomas and/or adenocarcinoma in female rats, and liver tumors in mice. Mutagenicity studies conducted with the technical spirodiclofen formulation and its major

metabolites did not demonstrate any mutagenic potential. Spirodiclofen has been shown to have adverse effects on several organs of the endocrine system at relatively low doses. Testicular effects were observed in dogs, rats, and mice, manifested as Leydig cell vacuolation in dogs, hypertrophy in dogs and mice, and hyperplasia progressing to adenomas in rats, following chronic exposure. In female rats, increased incidence of uterine nodules and uterine adenocarcinoma were observed at terminal sacrifice in the chronic toxicity study. Cytoplasmic vacuolation in the adrenal cortex, accompanied by increased adrenal weight, was consistently observed in rats, dogs, and mice of both sexes.

***Food Quality Protection Act (FQPA) Safety Factor (SF):*** The spirodiclofen toxicity database is adequate to evaluate the potential increased susceptibility of infants and children. The HED Hazard Identification Assessment Review Committee (HIARC; 2004) determined that there is no evidence (qualitative or quantitative) of increased susceptibility in the rabbit developmental toxicity study or in the rat reproduction toxicity study following *in utero* and/or pre-/post-natal exposure of spirodiclofen. However, evidence for quantitative susceptibility was observed in a rat developmental toxicity study where an increased incidence of slight dilatation of the renal pelvis was observed at a dose (1000 mg/kg/day; HDT) which did not cause any maternal toxicity. Two rat DNT studies were submitted to HED following the HIARC assessment in 2004. The first study demonstrated increased susceptibility in the offspring based on the observed decreased retention in the memory phase of the water maze for postnatal day 60 females at all doses (lowest-observable adverse-effect level (LOAEL) = 6.5 mg/kg/day) and changes in brain morphometric parameters at the HDT (135.9 mg/kg/day; caudate putamen, parietal cortex, hippocampal gyrus, and dentate gyrus); there was no maternal toxicity at doses up to and including 135.9 mg/kg/day (HDT). HED requested information concerning the brain morphometric parameters in the low and mid doses with the petitioner indicating that the brain tissues were not appropriately preserved and analysis was therefore not possible. As a result, a second rat DNT was submitted which also indicated increased susceptibility in offspring based on decreased pre-weaning body weight and body-weight gain in males and females and decreased post-weaning body weights in males (LOAEL = 119.2 mg/kg/day; no-observable adverse-effect level (NOAEL) = 28.6 mg/kg/day). Neurotoxicity was not observed in offspring in the second DNT study, and there was no maternal toxicity observed at doses up to and including 119.2 mg/kg/day.

HED determined that the degree of concern is low for the quantitative susceptibility seen in the developmental toxicity study in rats (observed at the limit-dose only without statistical significance and dose response). The two DNT studies suggest increased susceptibility of offspring due to exposure to spirodiclofen. However, there is no concern for the increased susceptibility seen in the first DNT study because the results were not reproduced in the second DNT study conducted using the identical doses and experimental conditions. The concern for increased susceptibility in the second DNT study is low because there is a well established NOAEL, marginal toxicity (slight changes in body weights), and all developmental/functional parameters were comparable to controls. In addition, doses selected for risk assessment of spirodiclofen are much lower than the doses that caused renal pelvic dilation seen in the rat devleopmental study and the marginal changes in the body weights of offspring in the second DNT study. There was no evidence of increased susceptibility in the developmental toxicity study in rabbits or the two-generation reproduction study in rats.

The FQPA SF of 3x has been retained for use of a LOAEL instead of NOAEL for short-term dermal and inhalation exposure scenarios. In addition, an immunotoxicity study has not been submitted as required in 40 CFR Part 158 for conventional pesticide registration. However, the Agency does not believe that conducting a functional immunotoxicity study will result in a lower point of departure (POD) than that currently used for overall risk assessment, and therefore, a database uncertainty factor ($UF_{DB}$) is not needed to account for the lack of this study (see page 12 for rationale). In addition, since the food/feed and water estimates used in the dietary exposure analysis are unlikely to underestimate exposure, the risk assessment team concluded that the FQPA SF (3X) was adequate. The table below is a summary of the PODs used as part of the current assessment.

| Exposure Scenario | Dose Used in Risk Assessment, UF | FQPA SF and Level of Concern for Risk Assessment | Study and Toxicological Effects |
|---|---|---|---|
| Acute Dietary | An appropriate endpoint attributable to a single dose was not identified. Assessment not necessary. | | |
| Chronic Dietary (All populations) | NOAEL= 1.38 mg/kg/day<br>UF = 100<br>cRfD = 0.014 mg/kg/day | FQPA SF = 1x<br>cPAD = cRfD ÷ FQPA SF = 0.014 mg/kg/day | Chronic Oral Toxicity Study in Dogs; LOAEL= 4.7 mg/kg/day based on increased relative adrenal weights in both sexes, increased relative testis weight in males and histopathology findings in the adrenal gland of both sexes. |
| Short-term Dermal and Inhalation (1-30 Days) | LOAEL = 8.4 mg/kg/day<br>dermal-absorption rate= 2% | Residential/Occupational LOC for MOE <300 | Subchronic Oral Toxicity Study in Dogs; LOAEL= 8.4 mg/kg/day based on increased adrenal gland weight (two out of four animals) which corroborated with histopathology findings (cytoplasmic vacuoles in the Zona fasciculata of the adrenal glands) in females; a NOAEL for females was not established. |
| Cancer; Oral, Dermal, Inhalation | Classification: "Likely to be Carcinogenic to Humans"; $Q_1^*$ $(mg/kg/day)^{-1} = 1.49 \times 10^{-2}$. | | |

UF = uncertainty factor. RfD = reference dose. LOC = level of concern. MOE = margin of exposure = NOAEL ÷ exposure. cPAD = chronic population adjusted dose.

***Dietary (food and water) Risk Assessment:*** Chronic and cancer dietary risk assessments were conducted using the Dietary Exposure Evaluation Model - Food Consumption Intake Database (DEEM-FCID™, ver. 2.03). Acute dietary risk assessment was not conducted since an appropriate endpoint attributable to a single dose was not identified for the general U.S. population or any population subgroup. The chronic and cancer analyses assumed the following: **(1)** average field trial residues; **(2)** experimentally determined processing factors for apple and grape processed commodities and for citrus oil, peeled citrus, and citrus peel (DEEM (ver 7.81) defaults assumed for the remaining processed commodities); **(3)** Biological and Economic Analysis Division (BEAD; D340691, J. Alsadek, August 2007) projected average percent crop treated estimates for hop (92%), pome fruit (15%), stone fruit (10%), grape (7%), and citrus (14%); **(4)** drinking water estimates derived from the Pesticide Root Zone/Exposure Analysis Modeling System (PRZM/EXAMS) model (citrus application scenario; 1 x 0.31 lb ai/acre); and **(5)** maximum reasonably balanced livestock diets. The resulting chronic risk estimates (food and water) were ≤3.3% cPAD and are not of concern to HED (infants (<1 year old) were the most highly exposed population). The cancer risk estimate (food and water) for the U.S. population was $3 \times 10^{-6}$.

HED is generally concerned when the cancer risk exceeds $10^{-6}$. Based on a critical commodity analysis conducted in DEEM-FCID™, the major contributors to the cancer risk were hops (40% of the total exposure), water (19% of the total exposure), and orange juice (16% of the total exposure). HED notes the following concerning the residue estimates for hop, water, and orange juice: **(1)** hop - DEEM-FCID™ assumes that 100% of the residue in hops are transferred to beer during the brewing process (no residue remain in/on the spent hops); based on the spirodiclofen log $K_{OW}$ of 5.83, this is a conservative assumption; in addition, assumed 92% crop treated for hops (average projected percent crop treated estimate); **(2)** water - the water residue estimate assumed 87% of the basin is cropped with 100% of the crops treated; and **(3)** orange juice - pending the submission of a new orange processing study, default citrus juice processing factors are to be assumed (D341847, T. Bloem, 25-Oct-2007); in addition, assumed 14% crop treated for orange juice (average projected percent crop treated estimate). Therefore, HED concludes that the cancer risk estimate provided in this assessment is conservative and actual cancer risk will be significantly lower than $3 \times 10^{-6}$.

***Aggregate Risk Assessment:*** The uses proposed as part of the current petition and the currently registered uses are not expected to result in residential exposure. Therefore, the chronic and cancer risk assessments provided in the Dietary Exposure Section represent aggregate risk.

***Occupational Risk Assessment:*** No chemical-specific handler exposure data were submitted in support of this Section 3 registration. It is the policy of the HED to use data from the Pesticide Handlers Exposure Database (PHED) Version 1.1 as presented in PHED Surrogate Exposure Guide (8/98) to assess handler exposures for regulatory actions when chemical-specific monitoring data are not available (HED Science Advisory Council for Exposure (ExpoSAC) Draft Standard Operating Procedure (SOP) # 7, dated 1/28/99).

Handler and post-application exposure is expected to be short-term based on information provided on proposed labels (e.g., only one application allowed per crop season). Airblast and aerial applications were assessed. All short-term risks for occupational handlers do not exceed HED's level of concern (i.e., MOEs >300) at baseline except for aerial handler (MOE = 93); acceptable aerial handler MOEs were calculated with the addition of single-layer gloves as specified on the label (12,000). All post-application risks are also not of concern (i.e., MOEs >300). Handler and post-application cancer risk estimates were below HED's level of concern with the addition of single-layer gloves as specified on the label (i.e., risks are below $1 \times 10^{-4}$).

The proposed label for ENVIDOR® has a 12- hour REI. Spirodiclofen is classified as Toxicity Category III for acute oral and acute dermal toxicity; and Toxicity Category IV for acute inhalation, primary eye irritation, and primary dermal irritation. It is a dermal sensitizer. Under the conditions described herein (i.e., regarding hazard identification and application practices), the interim worker-protection standard (WPS) REI of 12 hours is adequate to protect agricultural worker from post-application exposures.

***Environmental Justice:*** Potential areas of environmental justice concerns, to the extent possible, were considered in this human health risk assessment, in accordance with U.S. Executive Order 12898, "Federal Actions to Address Environmental Justice in Minority Populations and Low-Income Populations (http://www.hss.energy.gov/nuclearsafety/env/guidance/justice/eo12898.pdf).

As a part of every pesticide risk assessment, OPP considers a large variety of consumer subgroups according to well-established procedures. In line with OPP policy, HED estimates risks to population subgroups from pesticide exposures that are based on patterns of that subgroup's food and water consumption, and activities in and around the home that involve pesticide use in a residential setting. Extensive data on food consumption patterns are compiled by the USDA under the Continuing Survey of Food Intake by Individuals (CSFII) and are used in pesticide risk assessments for all registered food uses of a pesticide. These data are analyzed and categorized by subgroups based on age, season of the year, ethnic group, and region of the country. Additionally, OPP is able to assess dietary exposure to smaller, specialized subgroups and exposure assessments are performed when conditions or circumstances warrant (see below). Whenever appropriate, non-dietary exposures based on home use of pesticide products and associated risks for adult applicators and for toddlers, youths, and adults entering or playing on treated areas postapplication are evaluated. Further considerations are currently in development as OPP has committed resources and expertise to the development of specialized software and models that consider exposure to bystanders and farm workers as well as lifestyle and traditional dietary patterns among specific subgroups.

***Human Studies:*** This assessment relies in part on data from studies in which adult human subjects were intentionally exposed to a pesticide. These studies, which comprise PHED, have been determined to require a review of their ethical conduct, and received that review. The studies in PHED were considered appropriate (or ethically conducted) for use in risk assessments.

***HED Recommendation:*** Provided the petitioner submits revised Sections B and F, HED concludes that the toxicological, residue chemistry, and occupational/residential exposure databases support a conditional registration and establishment of the following permanent tolerances for residues of spirodiclofen *per se* (3-(2,4-dichlorophenyl)-2-oxo-1-oxaspiro[4.5]dec-3-en-4-yl 2,2-dimethylbutanoate): Avocado - 1.0 ppm, Black sapote - 1.0 ppm, Canistel - 1.0 ppm, Mamey sapote - 1.0 ppm, Mango - 1.0 ppm, Papaya - 1.0 ppm, Sapodilla - 1.0 ppm, and Star apple - 1.0 ppm.

Unconditional registration may be established upon submission of an immunotoxicity study which adequately addresses the data requirements specified in 40 CFR Part 158.

## 2.0 Ingredient Profile

Spirodiclofen is a tetronic acid with acaricidal action. It acts by interfering with mite development, thereby controlling such pests as *Panonychus* spp., *Phyllocoptruta* spp., *Brevipalpus* spp., and *Aculus* and *Tetranychus* species. Spirodiclofen is active by contact to mite eggs, all nymphal stages, and adult females (adult males are not affected).

## 2.1 Summary of Registered/Proposed Uses

***Registered:*** Spirodiclofen is currently registered for application to citrus fruit, grape, pome fruit, stone fruit, tree nuts, and hops with tolerances for residues of spirodiclofen *per se* of 0.10-30 ppm (1 x 0.16-0.53 lb ai/acre; PHI = 7-14 days); milk and ruminant meat, meat byproducts, and fat tolerances for the combined residues of spirodiclofen and BAJ 2510 are also established (0.02-0.1 ppm).

***Proposed:*** The petitioner provided proposed use directions for application of Envidor® 2 SC Miticide (2 lbs ai/gallon; EPA Reg. No. 264-831) to avocado, black sapote, canistel, mamey sapote, mango, papaya, sapodilla, and star apple (see Table 2.1.1 for summary). Application through irrigation equipment and in enclosed structures is prohibited. Although the label does not indicate that adjuvants (e. g.; crop-oil concentrate, nonionic surfactant, methylated seed oil) should be added to the spray solution, it does not prohibit the inclusion of adjuvants. Since the field trial data submitted in support of the proposed action did not include adjuvants, HED requests a revised Section B prohibiting the addition of adjuvants to the spray solution.

**Table 2.1.1: Summary of Proposed Application Scenarios.**

| Applic. Type | Max. Single App. Rate (lb ai/acre) | Max. No. App. per Season | PHI (days) | Comments |
|---|---|---|---|---|
| **Avocado, Black Sapote, Canistel, Mamey Sapote, Mango, Papaya, Sapodilla, and Star Apple** | | | | |
| foliar spray | 0.28-0.31 | 1 | 2 | •Excluding avocado, applications may be made with ground equipment only (minimum spray volume of 50 gallons per acre (GPA)); for avocado, the label states that ground (minimum spray volume of 50 GPA) or aerial (minimum spray volume of 100 GPA) application equipment may be used.<br>•Maximum seasonal application rate - 0.31 lb ai/acre.<br>•Label states the following pests are controlled - Avocado brown mite, Avocado red mite, Broad mite, Carmine spider mite, Citrus red mite, Flat mite (black and red), Mango spider mite, Papaya Leaf edgeroller mite, Persea mite, Sixspotted mite, Texas citrus mite, and Twospotted spider mite.<br>•12-hour REI.<br>•Label directs mixers, loaders, applicators and other handlers to wear a long-sleeve shirt, long pants, waterproof gloves and shoes plus socks. |

## 2.2 Structure and Nomenclature

Tables 2.2.1 and 2.2.2 are summaries of spirodiclofen nomenclature and physical chemical properties, respectively.

**Table 2.2.1: Nomenclature.**

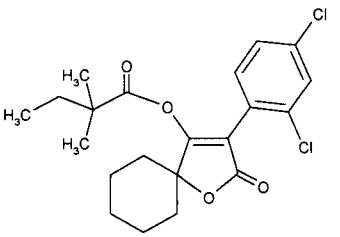
| | |
|---|---|
| Spirodiclofen |  |
| Common name | Spirodiclofen |
| Company experimental name | BAJ 2740 |
| IUPAC name | 3-(2,4-dichlorophenyl)-2-oxo-1-oxaspiro[4,5]dec-3-en-4-yl 2,2-dimethylbutyrate |
| CAS name | 3-(2,4-dichlorophenyl)-2-oxo-1-oxaspiro[4,5]dec-3-en-4-yl 2,2-dimethylbutanoate |
| CAS registry number | 148477-71-8 |
| End-use product (EP) | 2 lb/gal FlC (ENVIDOR® 2 SC Miticide; EPA Reg. No. 264-831) |

**Table 2.2.2: Physicochemical Properties of Spirodiclofen.**

| | | | |
|---|---|---|---|
| Melting point | 94.8°C | | D315459, S. Mathur, 20-Apr-2005 |
| pH | 4.2 | | |
| Density (20°C) | 1.29 g/cm$^3$ | | |
| Water solubility (20°C at pH 4) | 50µg/L | | |
| Solvent solubility (g/L at 20°C) | n-heptane | 20 | |
| | xylene | >250 | |
| | dichloromethane | >250 | |
| | 2-propanol | 47 | |
| | 1-octanol | 44 | |
| | polyethylene glycol | 24 | |
| | acetone | >250 | |
| | ethyl acetate | >250 | |
| | acetonitrile | >250 | |
| | dimethylsulfoxide | 75 | |
| Vapor pressure (20°C) | 3 x 10$^{-7}$ Pa | | |
| Dissociation constant, $pK_a$ | Not determinable due to the instability in aqueous solutions at >pH 4 | | |
| Log($K_{OW}$) at pH 4 and 20°C | 5.83 | | |
| UV/visible absorption spectrum | λmax = 201 nm: Not expected to absorb UV at λ >350 nm | | |

## 3.0 Hazard Characterization/Assessment

The toxicological database for spirodiclofen is adequate for FQPA evaluation, selection of PODs for the various routes of exposure, and for dose-response evaluation. The following is a summary of the spirodiclofen toxicological database. For a complete review of these data please refer to the human-health risk assessment D339672 (M. Clock-Rust *et al.*, 1-Apr-2008). Attachment 2 includes a tabular summary of the spirodiclofen acute, subchronic, and chronic toxicity profile.

## 3.1 Mammalian Toxicology

Spirodiclofen has a low acute toxicity *via* the oral, dermal, and inhalation routes. It is not an eye or dermal irritant. However, it is a potential skin sensitizer. Following oral administration, spirodiclofen is rapidly absorbed, metabolized, and excreted *via* urine and feces. A rat whole body autoradiography study showed no accumulation in any specific organs or tissues following oral administration. Evidence of developmental toxicity was not observed in the rabbit developmental study. The rat developmental study resulted in an increased incidence of slight dilatation of the renal pelvis (1000 mg/kg/day; HDT) at a dose which did not cause maternal toxicity. In the two-generation reproductive toxicity study, developmental effects were observed in $F_1$ males (i.e., delayed sexual maturation, decreased testicular spermatid and epididymal sperm counts (oligospermia); and atrophy of the testes, epididymides, prostate, and seminal vesicles) and $F_1$ females (i.e., increased severity of ovarian luteal cell vacuolation/degeneration) but at a higher dose (1750 ppm) than the systemic effects seen for parents and offspring (350 ppm). Spirodiclofen did not show any evidence of neurotoxicity in the acute and subchronic neurotoxicity studies. In a DNT study, a decrease in retention was observed in the memory phase of the water maze for PND 60 females at all doses. In this DNT study, the morphometric measurements were not performed at the low- and mid-dose; therefore, the registrant conducted a new study using identical experimental conditions as the previous study. The results of the new study demonstrated no treatment related maternal or offspring toxicity at the highest dose tested. Therefore, it can be concluded that spirodiclofen is unlikely to be a neurotoxic or developmentally-neurotoxic compound.

Chronic toxicity and carcinogenicity studies showed increased incidence of uterine adenocarcinoma in female rats, Leydig cell adenoma in male rats, and liver tumors in mice. The CARC classified spirodiclofen as "likely to be carcinogenic to humans" by the oral route based on evidence of testes Leydig cell adenomas in male rats, uterine adenomas and/or adenocarcinoma in female rats, and liver tumors in mice (TXR No. 0052552; 5-May-2004). Mutagenicity studies conducted with the technical spirodiclofen formulation and its major metabolites did not demonstrate any mutagenic potential. Spirodiclofen has been shown to have adverse effects on several organs of the endocrine system at relatively low doses. Testicular effects were observed in dogs, rats, and mice, manifested as Leydig cell vacuolation in dogs, hypertrophy in dogs and mice, and hyperplasia progressing to adenomas in rats, following chronic exposure. In female rats, increased incidence of uterine nodules and uterine adenocarcinoma were observed at terminal sacrifice in the chronic toxicity study. Cytoplasmic vacuolation in the adrenal cortex, accompanied by increased adrenal weight, was consistently observed in rats, dogs, and mice of both sexes.

## 3.2 FQPA SF

The spirodiclofen toxicity database is adequate to evaluate the potential increased susceptibility of infants and children. The HIARC (2004) determined that there is no evidence (qualitative or quantitative) of increased susceptibility in the rabbit developmental toxicity study or in the rat reproduction toxicity study following *in utero* and/or pre-/post-natal exposure of spirodiclofen (TXR 0052518, 16-Jun-2004). However, evidence for quantitative susceptibility was observed in a rat developmental toxicity study where an increased incidence of slight dilatation of the renal pelvis was observed at a dose (1000 mg/kg/day) which did not cause any maternal toxicity. Two rat DNT studies were submitted to HED following the HIARC assessment in 2004. The first study demonstrated increased susceptibility in the offspring based on the observed decreased retention in the memory phase of the water maze for postnatal day 60 females at all doses (LOAEL 6.5 mg/kg/day) and changes in brain morphometric parameters at the HDT (135.9 mg/kg/day; caudate putamen, parietal cortex, hippocampal gyrus, and dentate gyrus); there was no maternal toxicity at doses up to and including 135.9 mg/kg/day (HDT). HED requested information concerning the brain morphometric parameters in the low and mid doses with the petitioner indicating that the brain tissues were not appropriately preserved and analysis was therefore not possible. As a result, a second rat DNT was submitted which also indicated increased susceptibility in offspring based on decreased pre-weaning body weight and body-weight gain in males and females and decreased post-weaning body weights in males (LOAEL = 119.2 mg/kg/day; NOAEL = 28.6 mg/kg/day). Neurotoxicity was not observed in offspring in the second DNT study, and there was no maternal toxicity observed at doses up to and including 119.2 mg/kg/day.

HED determined that the degree of concern is low for the quantitative susceptibility seen in the developmental toxicity study in rats. The increased incidence of slight renal pelvic dilation was observed at the limit-dose only without statistical significance and dose response. Renal pelvic dilation was considered to be a developmental delay and not a severe effect for developmental toxicity. The low background incidences in this study may be idiosyncratic to this strain (Wistar) of rats since renal pelvis dilations are commonly seen at higher incidences in other strains (Sprague-Dawley or Fisher) of rats. In addition, doses selected for risk assessment of spirodiclofen are much lower than the dose that caused these developmental delays. The two DNT studies suggest increased susceptibility of offspring due to exposure to spirodiclofen. However, there is no concern for the increased susceptibility seen in the first DNT study because the results were not reproduced in the second DNT study conducted using the identical doses and experimental conditions. The concern for increased susceptibility in the second DNT study is low because there is a well established NOAEL, marginal toxicity (slight changes in body weights), and all developmental/functional parameters were comparable to controls. In addition, doses selected for risk assessment of spirodiclofen are much lower than the dose that caused these marginal changes in the body weights of offspring in the second DNT study. There was no evidence of increased susceptibility in the developmental toxicity study in rabbits or the two-generation reproduction study in rats.

The FQPA SF of 3x has been retained for use of a LOAEL instead of NOAEL for short-term dermal and inhalation exposure scenarios. HIARC (2004) determined that a 3x uncertainty factor is adequate (for the use of a LOAEL) since the extrapolated NOAEL (8.4/3= 2.8 mg/kg/day) in the subchronic dog study is comparable to the NOAEL (1.38 or 1.52 mg/kg/day for males or females, respectively) in the chronic dog study.

The toxicology database for spirodiclofen does not show any evidence of treatment-related effects on the immune system. The overall weight of evidence suggests that this chemical does not directly target the immune system. An immunotoxicity study is required as a part of new data requirements in the 40 CFR Part 158 for conventional pesticide registration; however, the Agency does not believe that conducting a functional immunotoxicity study will result in a lower POD than that currently used for overall risk assessment, and therefore, a database uncertainty factor ($UF_{DB}$) is not needed to account for the lack of this study. In addition, since the food/feed and water estimates used in the dietary exposure analysis are unlikely to underestimate exposure, the risk assessment team concluded that the 3X FQPA SF was adequate.

## 3.3 Toxicity Endpoint Selection

Table 3.3.1 is a summary of the toxicological doses and endpoints used as part of the current risk assessment. Attachment 3 contains a summary of all doses and endpoints used for spirodiclofen risk assessment.

**Table 3.3.1: Summary of Toxicological Doses and Endpoints.**

| Exposure Scenario | Dose Used in Risk Assessment, UF | FQPA SF and Level of Concern for Risk Assessment | Study and Toxicological Effects |
|---|---|---|---|
| Acute Dietary | An appropriate endpoint attributable to a single dose was not identified. Assessment not necessary. | | |
| Chronic Dietary (All populations) | NOAEL= 1.38 mg/kg/day<br>UF = 100<br>cRfD = 0.014 mg/kg/day | FQPA SF = 1x<br>cPAD = cRfD ÷ FQPA SF = 0.014 mg/kg/day | Chronic Oral Toxicity Study in Dogs; LOAEL= 4.7 mg/kg/day based on increased relative adrenal weights in both sexes, increased relative testis weight in males and histopathology findings in the adrenal gland of both sexes. |
| Short-term Dermal and Inhalation (1-30 Days) | LOAEL = 8.4 mg/kg/day<br>dermal-absorption rate= 2% | FQPA SF = 3x<br>Residential/Occupational LOC for MOE <300 | Subchronic Oral Toxicity Study in Dogs; LOAEL= 8.4 mg/kg/day based on increased adrenal gland weight (two out of four animals) which corroborated with histopathology findings (cytoplasmic vacuoles in the Zona fasciculata of the adrenal glands) in females; a NOAEL for females was not established. |
| Cancer; Oral, Dermal, and Inhalation | Classification: "Likely to be Carcinogenic to Humans"; $Q_1^*$ $(mg/kg/day)^{-1} = 1.49 \times 10^{-2}$. | | |

UF = uncertainty factor. RfD = reference dose. LOC = level of concern. MOE = margin of exposure = NOAEL ÷ exposure.

## 3.4 Endocrine Disruption

EPA is required under the FFDCA, as amended by FQPA, to develop a screening program to determine whether certain substances (including all pesticide active and other ingredients) *"may have an effect in humans that is similar to an effect produced by a naturally occurring estrogen, or other such endocrine effects as the Administrator may designate."* Following the recommendations of its Endocrine Disruptor Screening and Testing Advisory Committee (EDSTAC), EPA determined that there were scientific bases for including, as part of the program, androgen and thyroid hormone systems, in addition to the estrogen hormone system. EPA also adopted EDSTAC's recommendation that the Program include evaluations of potential effects in wildlife. When the appropriate screening and/or testing protocols being considered under the Agency's Endocrine Disrupter Screening Program (EDSP) have been developed and vetted, spirodiclofen may be subjected to additional screening and/or testing to better characterize effects related to endocrine disruption.

## 4.0. Dietary Exposure/Risk Characterization

## 4.1 Metabolism in Primary Crops, Livestock, and Rotational Crops

The petitioner previously submitted citrus, grape, apple, and goat metabolism studies. Based on these data, the apple and grape processing studies, and information concerning environmental degradation of spirodiclofen, HED concluded that the residue of concern in plants, ruminants, and drinking water are as defined in Table 5.1.1. In addition, HED concluded that the metabolites/degradates included in the spirodiclofen risk assessment are not likely to be more toxic than parent. For further information concerning these conclusions, see the following documents: Risk Assessment Document - D285047, M. Clock-Rust *et al*, 22-Jun-2005; residue chemistry reviews - D341847, T. Bloem, 25-Oct-2007 and D359773, T. Bloem, 24-Jun-2009).

**Table 5.1.1: Residues of Concern for Tolerance Expression and Risk Assessment.**

| Matrix | Residues included in Risk Assessment | Residues included in Tolerance Expression |
|---|---|---|
| Proposed/Registered Fruit Crops, Hops, and Tree Nuts[1] | spirodiclofen | spirodiclofen |
| Grape[1] | spirodiclofen | spirodiclofen, BAJ 2510 |
| Livestock - Ruminants | spirodiclofen, BAJ 2510 | spirodiclofen, BAJ 2510 |
| Livestock - Poultry | no data submitted | |
| Rotational Crops | no data submitted | |
| Drinking Water | spirodiclofen, BAJ 2510, BAJ 2740-dihydroxy, BAJ 2740-ketohydroxy | not applicable |

[1] Pending the submission of the orange processing data, human-health risk assessments should assume default processing factors for all processed commodities excluding the processed commodities for apple and grape (D341847, T. Bloem, 25-Oct-2007).

## 4.2 Analytical Methodology

HED determined that the Bayer analytical method 109351 was appropriate for enforcement of the hop, citrus, grape, pome fruit, stone fruit, and tree nut tolerances and forwarded this method to Food and Drug Administration (FDA) for inclusion in the Pesticide Analytical Manual (PAM; D368434, T. Bloem, 23-Sep-2009). Based on the similarities of the data collection method and the tolerance enforcement method and since the tolerance enforcement method has been validated on a fruit crop, HED concludes that the current enforcement method is appropriate for enforcement of the tolerances recommended as part of this petition.

## 4.3 Comparative Metabolic Profile

The metabolic pathway in the proposed/registered primary crops, ruminant, and rat were similar and involved cleavage of the parent ester linkage with the formation of the free enol metabolite (BAJ 2510) followed by hydroxylation of the cyclohexane ring of BAJ 2510. In the rat and in the proposed crops, metabolism continued with cleavage of the enol ring structure leading to the formation of 2,4-dichloromandelic acid-cyclohexylester compounds which are further metabolized to 2,4-dichloromandelic acid derivatives (see Attachment 1 for structures).

## 4.4 Drinking Water Residue Profile

The major routes of degradation for spirodiclofen in the laboratory studies were hydrolysis, photolysis in water, and metabolism. Spirodiclofen is expected to be moderately persistent in the soil (half-life of 10-64 days), but dissipate rapidly from aquatic environments (half-life of 1-7 days). The major residue identified in the aerobic soil and anaerobic/aerobic aquatic degradation studies was BAJ 2510 (52-95% the applied dose at intervals of ≤56 days; EFED refers to this compound as BAJ 2740-enol). The aerobic soil degradation study also resulted in significant residues of BAJ 2740-dihydroxy (17% of the applied dose at an interval of 120 days), BAJ 2740-ketohydroxy (44% of the applied dose at 30 days), and DCB-acid (40% of the applied dose at 120 days). The aquatic photolysis study resulted in significant residues of BAJ 2740-dioxoketone (26% of the applied dose after an interval of 1 day). Under terrestrial field conditions, the major transformation products of spirodiclofen were BAJ 2510, BAJ 2740-ketohydroxy, BAJ 2740-dihydroxy, and DCB-acid. Spirodiclofen is expected to be immobile in soil ($K_{oc}$ range 31,037 to 238,000) while the identified degradation products are expected to be mobile.

HED determined that aquatic photolysis is not expected to be an important degradation route and, therefore, concluded that BAJ 2740-dioxoketone is not of concern in drinking water. In addition, HED concluded that DCB-acid is likely to be significantly less toxic than spirodiclofen and, therefore, this compound was excluded from the risk assessment. Based on the currently available data, HED concludes that the residues of concern in drinking water for purposes of risk assessment are spirodiclofen, BAJ 2510, BAJ 2740-dihydroxy, and BAJ 2740-ketohydroxy.

Surface and ground estimated drinking water concentrations were previously generated by EFED using PRZM-EXAMS and Screening Concentration in Ground Water Model (SCI-GROW), respectively (D311291, F. Kahn, 4-Jan-2005). The SCI-GROW model was run using the highest application rate (1 x 0.53 lb ai/acre) and resulted in a point estimate of 0.44 ppb. Multiple crop scenarios were modeled using PRZM-EXAMS (citrus, pecan, apple, peach, and grape; 87% cropped and 100% crop treated assumed) with citrus (1 x 0.31 lb ai/acre) resulting in the highest 1-in-10-year peak concentration (23.86 ppb), 1-in-10-year yearly average (4.99 ppb), and 30-year average (1.67 ppb). Since the applications rates proposed as part of the current petition are identical to the citrus application rate, HED concludes that the previously generated water estimates remain relevant. Therefore, the chronic and cancer analyses employed the citrus 1-in-10-year yearly average (4.99 ppb) and 30-year average (1.67 ppb), respectively.

## 4.5 Food Residue Profile

D363343, T. Bloem, 23-Sep-2009

***Primary Crops:*** In support of the proposed registration, five avocado field trials, conducted during 2007 and 2008 in the North American Free Trade Agreement (NAFTA) zones 3 (n=1) and 10 (n=4), were submitted. Provided a revised Section B is submitted which prohibits the addition of adjuvants to the spray solution, the application scenario employed in the field trials supports the proposed application scenario and resulted in spirodiclofen *per se* residues in/on avocado fruit of <0.01-0.614 ppm (method and storage intervals were adequately validated). The geographical representation of the field trial data conform to the data requirements specified in OPPTS 860.1500 for avocado. Based on the avocado field trial data and the tolerance calculator, HED concludes that an avocado tolerance of 1.0 ppm, for residues of spirodiclofen *per se*, is appropriate. Based on guidance from the HED Chemistry Science Advisory Council (ChemSAC), HED will translate the avocado field trial data to black sapote, canistel, mamey sapote, mango, papaya, sapodilla, and star apple (Reviewer's Guide and Summary of HED ChemSAC Approvals for Amending Commodity Definitions [40CFR § 180.1(h)] and Crop Group/Subgroups [40 CFR § 180.41]; B. Schneider; 14-Jun-2002). Therefore, the avocado residue data supports a tolerance of 1.0 ppm for residues of spirodiclofen *per se* in/on black sapote, canistel, mamey sapote, mango, papaya, sapodilla, and star apple. A revised Section F is requested.

***Livestock:*** Based on the revised Table 1 feedstuffs (OPPTS 860.1000), none of the proposed crops have feed commodities; therefore a discussion concerning the nature/magnitude of the residue in livestock is unnecessary.

***Rotational Crops:*** Since all of the requested crops are perennials, a discussion concerning the nature/magnitude of the residue in rotational crops is unnecessary.

## 4.6 International Residue Limits and HED-Recommended Tolerances

Table 4.6.1 is a summary of the proposed and recommended tolerances for residues of spirodiclofen *per se*. A revised Section F should be submitted. There are no Codex, Canadian, or Mexican maximum residue limits (MRLs) in/on the requested crops. Therefore, harmonization is not an issue for this registration.

**Table 4.6.1: Tolerance Summary.**

| Commodity | Proposed Tolerance (ppm) | HED-Recommended Tolerance (ppm) | Comments |
|---|---|---|---|
| Avocado | 1.3 | 1.0 | A revised Section F, specifying the correct tolerance value, is requested. |
| Black Sapote | 1.3 | 1.0 | |
| Canistel | 1.3 | 1.0 | |
| Mamey Sapote | 1.3 | 1.0 | |
| Mango | 1.3 | 1.0 | |
| Papaya | 1.3 | 1.0 | |
| Sapodilla | 1.3 | 1.0 | |
| Star Apple | 1.3 | 1.0 | |

## 4.7 Dietary Exposure and Risk

D363344, T. Bloem, 23-Sep-2009

Chronic and cancer dietary risk assessments were conducted using the DEEM-FCID™ (ver. 2.03). Acute dietary risk assessment was not conducted since an appropriate endpoint attributable to a single dose was not identified for the general U.S. population or any population subgroup. The chronic and cancer analyses assumed the following: **(1)** average field trial residues; **(2)** experimentally determined processing factors for apple and grape processed commodities and for citrus oil, peeled citrus, and citrus peel (DEEM (ver 7.81) defaults assumed for the remaining processed commodities); **(3)** BEAD (D340691, J. Alsadek, August 2007) projected average percent crop treated estimates for hop (92%), pome fruit (15%), stone fruit (10%), grape (7%), and citrus (14%); **(4)** drinking water estimates derived from the PRZM/EXAMS model (citrus application scenario; 1 x 0.31 lb ai/acre); and **(5)** maximum reasonably balanced livestock diets. The resulting chronic risk estimates (food and water) were ≤3.3% cPAD and are not of concern to HED (infants (<1 year old) were the most highly exposed population). The cancer risk estimate (food and water) for the U.S. population was $3 \times 10^{-6}$. Tables 5.2.1 and 5.2.2 are summaries of the chronic and cancer exposure analyses, respectively.

HED is generally concerned when the cancer risk exceeds $10^{-6}$. Based on a critical commodity analysis conducted in DEEM-FCID™, the major contributors to the cancer risk were hops (40% of the total exposure), water (19% of the total exposure), and orange juice (16% of the total exposure). Based on the conservative residue estimates for these three commodities (see below), HED concludes that the cancer risk estimate provided in this assessment is conservative and the actual cancer risk will be significantly lower than $3 \times 10^{-6}$.

•**Hop** - DEEM-FCID™ assumes that 100% of the residue in hops are transferred to beer during the brewing process (no residue remain in/on the spent hops); based on the spirodiclofen log $K_{OW}$

of 5.83, this is a conservative assumption; in addition, assumed 92% crop treated for hops (average projected percent crop treated estimate).

- **Drinking Water** - The water residue estimate assumed 87% of the basin is cropped with 100% of the crops treated.
- **Orange Juice** - Pending the submission of a new orange processing study, default citrus juice processing factors are to be assumed (grape and apple processing studies resulted in a reduction in residues in juice; D341847, T. Bloem, 25-Oct-2007); in addition, assumed 14% crop treated for all orange juice (average projected percent crop treated estimate).

HED notes that Pesticide Data Program (PDP) monitoring data are available for spirodiclofen in/on almonds, apple juice, raisin, and heavy cream (<LOD residues in/on all samples). Since these commodities contributed only 4% to the total cancer exposure estimate, it was determined that incorporation of these data into the dietary analysis were unnecessary.

**Table 5.2.1: Summary of Chronic Dietary Exposure and Risk.**

| Population Subgroup | cPAD (mg/kg/day) | Exposure (mg/kg/day) | %cPAD |
|---|---|---|---|
| General U.S. Population | 0.014 | 0.000256 | 1.8 |
| **All Infants (< 1 year old)** | | **0.000455** | **3.3** |
| Children 1-2 years old | | 0.000432 | 3.1 |
| Children 3-5 years old | | 0.000351 | 2.5 |
| Children 6-12 years old | | 0.000213 | 1.5 |
| Youth 13-19 years old | | 0.000162 | 1.2 |
| Females 13-49 years old | | 0.000201 | 1.4 |
| Adults 20-49 years old | | 0.000283 | 2.0 |
| Adults 50+ years old | | 0.000213 | 1.5 |

**Table 5.2.2: Summary of Cancer Dietary Exposure and Risk.**

| Population Subgroup | $Q_1$* | Exposure (mg/kg/day) | Risk |
|---|---|---|---|
| General U.S. Population | 0.0149 | 0.000186 | $3 \times 10^{-6}$ |

## 5.0 Residential (Non-Occupational) Risk

HED does not anticipate residential exposure from the proposed/registered uses. However, spray drift is always a potential source of exposure to residents nearby to spraying operations. This is particularly the case with aerial application, but, to a lesser extent, could also be a potential source of exposure from the ground application method additionally employed for spirodiclofen. The Agency has been working with the Spray Drift Task Force, EPA Regional Offices, and State Lead Agencies for pesticide regulation and other parties to develop the best spray drift management practices. The Agency is now requiring interim mitigation measures for aerial applications that must be placed on product labels/labeling. The Agency has completed its evaluation of the new database submitted by the Spray Drift Task Force, a membership of U.S. pesticide registrants, and is developing a policy on how to appropriately apply the data and the AgDRIFT computer model to its risk assessments for pesticides applied by air, orchard airblast, and ground hydraulic methods. After the policy is in place, the Agency may impose further refinements in spray drift management practices to reduce off-target drift and risks associated with aerial as well as other application types where appropriate.

## 6.0 Aggregate Risk Assessment

In accordance with the FQPA, HED must consider and aggregate pesticide exposures and risks from three major sources: food, drinking water, and residential exposures. The proposed/registered spirodiclofen uses are not expected to result in residential exposure. Therefore, the chronic and cancer dietary (food and water) risk assessments provided in the Dietary Exposure Section (Section 4.7) represent aggregate risk.

## 7.0 Cumulative Risk Characterization/Assessment

Unlike other pesticides for which EPA has followed a cumulative risk approach based on a common mechanism of toxicity, EPA has not made a common mechanism of toxicity finding for spirodiclofen and any other substances; and spirodiclofen does not appear to produce a toxic metabolite produced by other substances. For the purposes of this tolerance action, therefore, EPA has assumed that spirodiclofen does not have a common mechanism of toxicity with other substances. For information regarding EPA's efforts to determine which chemicals have a common mechanism of toxicity and to evaluate the cumulative effects of such chemicals, see the policy statements released by EPA's Office of Pesticide Programs concerning common mechanism determinations and procedures for cumulating effects from substances found to have a common mechanism on EPA's website at http://www.epa.gov/pesticides/cumulative/.

## 8.0 Occupational Exposure/Risk Pathway

D363346, L. Venkateshwara, 23-Sep-2009

Spirodiclofen is proposed for a single application to avocado, black sapote, canistel, mamey sapote, mango, papaya, sapodilla, and star apple at 0.31 lb ai/acre (PHI = 2 days; REI = 12 hours; see Section 2.1). Based on the proposed application scenario and toxicological considerations, handler (short-term dermal and inhalation; see Section 8.1), post-application (short-term dermal and inhalation; see Section 8.2), and cancer (handler and post-application, see Section 8.3) risk assessment were conducted.

### 8.1 Short-Term Handler Exposure and Risk Estimates

There is potential for the following occupational handler exposure from the proposed uses: **(1)** mixing/loading liquids for airblast and aerial applications; **(2)** applying sprays via airblast and aerial equipment; and **(3)** flagging to support aerial applications.

No chemical-specific data were available with which to assess potential exposure to pesticide handlers. The pesticide handler exposure estimates are based upon the surrogate study data available in PHED (August, 1998). For pesticide handlers, HED presents estimates of dermal exposure for "baseline" (i.e., workers wearing a single layer of work clothing consisting of a long-sleeved shirt, long pants, shoes plus socks, and no protective gloves), as well as for "baseline" and the use of protective gloves or other personal-protective equipment (PPE), as might be necessary. HED note that the proposed spirodiclofen product label directs mixers, loaders, applicators and other handlers to wear a long-sleeve shirt, long pants, waterproof gloves, and shoes plus socks.

Handler exposure is expected to be short-term in duration (1-30 days) based on information provided on the proposed label (e.g., only one application allowed per crop season). HED has no data to assess exposures to pilots using open cockpits. The only data available for exposure to pilots is in enclosed cockpits. Therefore, risks to pilots are assessed using the engineering control (enclosed cockpits) and baseline attire (long-sleeve shirt, long pants, shoes and socks); pilots are not required to wear gloves.

Table 8.1.1 presents the estimated risks for handlers based on the short-term dermal and inhalation exposures with baseline attire, or with additional PPE. HED has determined that risks are not of concern for short-term exposures (i.e., MOEs >300) when handlers wear the PPE required on the label.

**Table 8.1.1: Short-Term Occupational Handler Risk Estimates.**

| Dermal and Inhalation Unit Exposures (mg/lb ai) | App. rate (lb ai/acre)[1] | Area Treated Daily (acre)[2] | Short-term Doses (mg/kg/day)[3] | | Short-term MOEs[4] | |
|---|---|---|---|---|---|---|
| ***Mixer/Loader – Airblast Application*** | | | | | | |
| Dermal<br>Baseline[5]: 2.9<br>Inhalation<br>Baseline[6]: 0.0012 | 0.31 | 40 | Dermal<br>Baseline: 0.01<br>Inhalation<br>Baseline: 0.0002 | Combined<br>Baseline: 0.01 | Dermal<br>Baseline: 820<br>Inhalation<br>Baseline: 40,000 | Combined<br>Baseline: 800 |
| ***Mixer/Loader – Aerial Application*** | | | | | | |
| Dermal<br>Baseline: 2.9<br>SLWG[8]: 0.023<br>Inhalation<br>Baseline: 0.0012 | 0.31 | 350 | Dermal<br>Baseline: 0.09<br>SLWG: 0.00071<br>Inhalation<br>Baseline: 0.002 | Combined<br>Baseline: 0.092<br>Combined<br>SLWG: 0.0027 | Dermal<br>Baseline: 93<br>SLWG: 12,000<br>Inhalation<br>Baseline: 4,500 | Combined<br>Baseline: 92<br>Combined<br>SLWG: 3,300 |
| ***Applicator –Airblast Application*** | | | | | | |
| Dermal<br>Baseline: 0.36<br>Inhalation<br>Baseline: 0.0045 | 0.31 | 40 | Dermal<br>Baseline: 0.0013<br>Inhalation<br>Baseline: 0.0008 | Combined<br>Baseline: 0.0021 | Dermal<br>Baseline: 6,600<br>Inhalation<br>Baseline: 11,000 | Combined<br>Baseline: 4,100 |
| ***Applicator –Aerial Application*** | | | | | | |
| Dermal<br>Engineering Control[7]: 0.005<br>Inhalation<br>Engineering Control[7]: 0.000068 | 0.31 | 350 | Dermal<br>Engineering Control: 0.00016<br>Inhalation<br>Engineering Control: 0.00011 | Combined<br>Engineering control: 0.00027 | Dermal<br>Engineering Control: 54,000<br>Inhalation<br>Engineering Control: 80,000 | Combined<br>Engineering control: 32,000 |
| ***Flagger –Aerial Application*** | | | | | | |
| Dermal<br>Baseline: 0.011<br>Inhalation<br>Baseline: 0.00074 | 0.31 | 350 | Dermal<br>Baseline: 0.00034<br>Inhalation<br>Baseline: 0.00054 | Combined<br>Baseline: 0.0009 | Dermal<br>Baseline: 25,000<br>Inhalation<br>Baseline: 15,000 | Combined<br>Baseline: 9,500 |

[1] Application rates are the maximum (single) recommended rates provided on the proposed label.

[2] Area treated per day values are HED estimates based on ExpoSAC Policy #9 "Standard Values for Daily Acres Treated in Agriculture," industry sources, and HED estimates.

[3] Dose (mg/kg/day) = (Unit exposure(mg/lb ai) x App Rate (lb ai/acre) x Area Treated (acres/day) x %Absorption (2% dermal and 100% inhalation assumed)) ÷ Body weight (70 kg).

[4] MOE = NOAEL or LOAEL/Dose; where the short-term dermal and inhalation LOAEL = 8.4 mg/kg/day.

[5] Baseline Dermal: Long-sleeve shirt, long pants, and no gloves.

[6] Baseline Inhalation: no respirator.

[7] Eng Con Dermal and Inhalation Engineering control for the aerial application scenario is an enclosed cockpit and baseline attire (long-sleeve shirt, long pants, shoes, and socks).

[8] PPE - SLWG = Single layer plus chemical-resistant gloves.

## 8.2 Short-Term Post-application Exposure and Risk Estimates

Based on the proposed crops and application scenario, HED concluded that thinning and harvesting are the post-application activities which may result in occupational exposure; exposures were assessed using previously submitted spirodiclofen dislodgeable foliar residue (DFR) data (see below) as well as dermal transfer coefficients from HED's ExpoSAC Policy Number 3.1 "Agricultural Transfer Coefficients" (August, 2000). HED concluded that the apple DFR data is an appropriate surrogate for the assessment of post-application exposure to the proposed crops (proposed crops are all fruit tree crops). Since only a single application is permitted per season, only short-term post-application exposure is expected.

HED has determined that short-term risk estimates are not of concern (i.e., MOEs >300) on the day of treatment (i.e., Day 0) for all postapplication exposure activities. Table 8.2.2 presents a summary of occupational postapplication risks associated with the proposed use of spirodiclofen (the information in the table is based on proprietary and non-proprietary data).

***DFR Study:*** A DFR study was submitted to the Agency by Bayer Corporation which examined the dissipation of residues on citrus and apple trees following application of spirodiclofen (ENVIDOR® 2 SC Miticide). The study was reviewed by HED and deemed acceptable for use in occupational post-application risk assessments (D285247, M. Dow, 29-Jun-2004). In the study, there were three test sites for citrus (California, Florida, and Texas) and two apple test sites (Washington and Ontario, Canada). A single application was made at all test sites using typical, orchard, airblast equipment. Maximum residues were identified at the Washington site for apples (0.11 lb ai/acre) and these values were used to estimate post-application exposure from treatment of tropical fruit. The data from this site demonstrated a steady decline in the DFR as the interval from treatment increased from 0 (0.169 $\mu g/cm^2$) to 30 days (0.083 $\mu g/cm^2$). Since the label indicates a 12-hour REI, post-application exposures were calculated using the 0-day DFR adjusted for the proposed application rate (0.31 lb ai/acre; 0.476 $\mu g/cm^2$). HED notes that the post-application cancer analysis (see below) incorporated the average DFR from this site adjusted for application rate (0.34 $\mu g/cm^2$).

**Table 8.2.2: Short-Term Post-application Risk Estimates for Spirodiclofen[1].**

| Crop | App. Rate (lb ai/acre) | Activitiy | Transfer Coefficient ($cm^2$/hr) | DFR ($\mu g/cm^2$) | Days After Treatment | Daily Dose[2] (mg/kg/day) | MOE[3] |
|---|---|---|---|---|---|---|---|
| avocado, black sapote, canistel, mamey sapote, mango, papaya, sapodilla, and star apple | 0.31 | harvesting | 1,500 | 0.476 | 0 (12 hours) | 0.0016 | 5,100 |
| | | thinning | 3,000 | | | 0.003 | 2,600 |

[1] The information in the table is based on proprietary and non-proprietary data.
[2] Daily Dose = (DFR ($\mu g/cm^2$) x TC ($cm^2$/hr) x 0.001 mg/$\mu g$ x Dermal Absorption (2%) x 8 hrs/day) ÷ Body Weight (70 kg).
[3] MOE = LOAEL/Daily Dose (Short-term LOAEL = 8.4 mg/kg/day).

## 8.3 Cancer Exposure and Risk Estimates

Cancer risk estimates resulting from exposures to spirodiclofen were calculated using a linear low-dose extrapolation approach in which a lifetime average daily dose (LADD) is multiplied by the $Q_1$*. The average daily dose (handler) or daily dose (post-application) values, amortized over a working lifetime, were used as the basis for calculating the LADD values. Since HED does not have information concerning typical application rates, the cancer assessment assumed the maximum application rate. Generally, HED considers occupational cancer risk estimates in the $10^{-6}$ to $10^{-4}$ range to be not of concern.

### 8.3.1 Handler Cancer Exposure and Risk Estimates

Based on the proposed application scenario (single application per season) and use patterns, it is anticipated that commercial applicators would apply spirodiclofen approximately 30 days per year. It was estimated that an individual farmer would handle spirodiclofen approximately 10 days per year. As a result, HED considered two handler populations (commercial and private handlers) for the cancer risk assessment. Finally, a 35-year career and a 70-year lifespan were used to complete the calculations.

Estimated spirodiclofen cancer risks for handlers are summarized in Table 8.3.1.1. In most scenarios, estimated cancer risks are below below $1 \times 10^{-6}$ at some level of risk mitigation. All cancer risk estimates are below $1 \times 10^{-4}$ with the single layer clothing, gloves, and no respiratory protection. Therefore, there are no concerns for occupational cancer risk for handlers.

**Table 8.3.1.1: Handler Cancer Risk Estimates for Commercial Spirodiclofen Handlers.**

| Scenario | Mitigation | Dermal Dose[1] (mg/kg/day) | Inhalation Dose[1] (mg/kg/day) | Combined ADD[2] (mg/kg/day) | LADD[3] (mg/kg/day) | Cancer Risk[4] |
|---|---|---|---|---|---|---|
| **Commercial** | | | | | | |
| | | | **Mixer/Loader** | | | |
| Mixing/loading liquids airblast application (1) | Baseline Dermal and Inhalation | 0.01 | 0.0002 | 0.01 | 4.3E-04 | 6.4E-06 |
| | Single layer w/gloves + Baseline Inhalation | 0.000081 | | 0.00029 | 1.2E-05 | 1.8E-07 |
| Mixing/loading liquids for aerial application (2) | Baseline Dermal and Inhalation | 0.09 | 0.002 | 0.092 | 3.8E-03 | 5.6E-05 |
| | Single layer w/gloves + Baseline Inhalation | 0.00071 | | 0.0027 | 0.00011 | 1.6E-06 |
| | | | **Applicator** | | | |
| Applying spray using airblast (3) | Baseline Dermal and Inhalation | 0.0013 | 0.0008 | 0.0021 | 8.5E-05 | 1.3E-06 |
| Applying spray using aerial (4) | Engineering Controls Dermal and Inhalation | 0.00016 | 0.00011 | 0.00027 | 1.1E-05 | 1.6E-07 |
| | | | **Flagger** | | | |
| Flagging during aerial application (5) | Baseline Dermal and Inhalation | 0.00034 | 0.0005 | 0.0009 | 3.6E-05 | 5.4E-07 |
| **Private** | | | | | | |
| | | | **Mixer/Loader** | | | |
| Mixing/loading liquids airblast application (1) | Baseline Dermal and Inhalation | 0.01 | 0.0002 | 0.01 | 1.4E-04 | 2.1E-06 |
| Mixing/loading liquids for aerial application (2) | Baseline Dermal and Inhalation | 0.09 | 0.0002 | 0.092 | 1.3E-03 | 1.9E-05 |
| | Single layer w/ gloves + BaselineInhalation | 0.00071 | | 0.0027 | 3.5E-05 | 5.3E-07 |
| | | | **Applicator** | | | |
| Applying spray using airblast (3) | Baseline Dermal and Inhalation | 0.0013 | 0.0008 | 0.0021 | 2.8E-05 | 4.2E-07 |
| Applying spray using aerial (4) | Engineering Controls Dermal and Inhalation | 0.00016 | 0.00011 | 0.00027 | 3.6E-06 | 5.3E-08 |
| | | | **Flagger** | | | |
| Flagging during aerial application (5) | Baseline Dermal and Inhalation | 0.00034 | 0.0005 | 0.0009 | 1.2E-05 | 1.8E-07 |

[1] Dermal Dose and Inhalation Doses (mg/kg/day) = See Table 8.1.1.
[2] Combined ADD (mg/kg/day) = Dermal Dose (mg/kg/day) + Inhalation Dose (mg/kg/day).
[3] LADD (mg/kg/day) = ADD x ((30 days/yr) ÷ (365 days/yr)) x (35 yrs ÷ 70yrs).
[4] Cancer Risk = LADD x Q*.

### 8.3.2 Occupational Post-application Cancer Exposure and Risk Estimates

Based on the proposed application scenario (single application per season) and use patterns, it is anticipated that individuals employed by multiple establishments (i.e., commercial or migratory farmworkers) could have post-application exposure up to 30 days per year. As indicated above, spirodiclofen DFR data have been submitted and were determined to be acceptable (see above for summary of these data; D285247, M. Dow, 29-Jun-2004). This study presented DFR data from 0 to 30 days after treatment; since only a single application is permitted and since 30 days per year of exposure are anticipated, the post-application cancer risk assessment incorporated the average DFR from this study.

Estimated spirodiclofen cancer risks for post-application exposure are summarized in Table 8.3.2.1. The estimated cancer risks are below or equal to $1 \times 10^{-6}$. Therefore, there are no conserns for occupational cancer risk for post-application workers.

**Table 8.3.2.1: Cancer Exposure/Risk Estimates for Spirodiclofen Post-application Workers.**

| Crop | DAT[1] | DFR[2] ($ug/cm^2$) | Transfer Coefficient[3] ($cm^2/hr$) | Daily Dose[4] (mg/kg/day) | LADD[5] | Cancer Risk[6] |
|---|---|---|---|---|---|---|
| avocado, black sapote, canistel, mamey sapote, mango, papaya, sapodilla, and star apple | 1 - 30 | 0. 34 | 1,500 | 0.0012 | 0.000048 | 7.14E-07 |
| | | | 3,000 | 0.0023 | 0.000096 | 1.43E-06 |

[1] DAT= 30 day residue average.
[2] DFR value used is based on a DFR study submitted to the Agency by Bayer Corporation in 2004.
[3] Transfer Coefficients selected in accordance with SAC for Exposure Policy 3.1 (August 2000).
[4] Daily Dose (DD; mg/kg/day)= DFR ($\mu g/cm^2$) x 0.001 mg/ug x Tc ($cm^2/hr$) x DA (2%) x ET (8 hr/day)/70 kg.
[5] LADD (mg/kg/day) = DD x ((30 days/yr)/ (365 days/yr)) x (35 yrs/70yrs).
[6] Cancer Risk = LADD x Q*.

## 8.4 REI

Spirodiclofen is classified in Acute Toxicity Category III for acute oral and acute dermal toxicity and Acute Toxicity Category IV for acute inhalation, primary eye irritation and primary skin irritation. It is a dermal sensitizer. The interim WPS REI of 12 hours is adequate to protect workers performing thinning and harvesting activities in the proposed crops. The proposed label is in compliance with the WPS REI.

## 9.0 Data Needs and Label Requirements

### 9.1 Toxicology

•The HIARC requested a 28-day rat inhalation toxicity study (TXR 0052518, 16-Jun-2004). Based on the low volatility and low inhalation toxicity (Category IV) of spirodiclofen and inhalation MOEs >1000 for the proposed use, **the requirement for the 28-day inhalation toxicity study is waived for this action only** (HED SOP 2002.01: *Guidance: Waiver Criteria for Multiple-Exposure Inhalation Toxicity Studies*; 15-Aug-2002).
•Immunotoxicity study as specified in 40 CFR Part 158.

### 9.2 Residue Chemistry

•Revised Sections B and F.

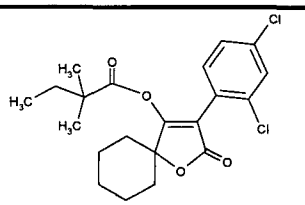
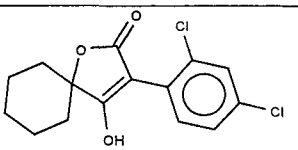
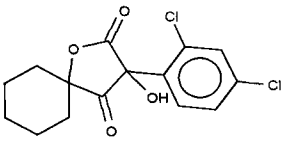
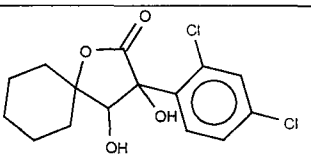
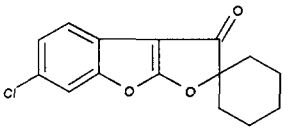
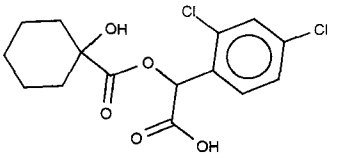
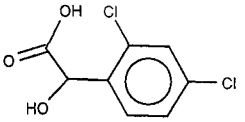
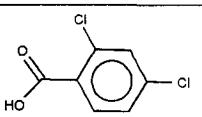
### 9.3 Occupational and Residential Exposure

•None.

Attachment 1: Chemical Names and Structures.
Attachment 2: Spirodiclofen Toxicity Profile.
Attachment 3: Summary of Toxicological Doses and Endpoints.

RDI: RAB1 review (30-Sep-2008)
T. Bloem:S10945:PY1:(703)-605-0217(7509P)

## Attachment 1: Chemical Names and Structures.

| Chemical Name | Structure |
|---|---|
| Spirodiclofen; BAJ 2740<br><br>3-(2,4-dichlorophenyl)-2-oxo-1-oxaspiro[4,5]dec-3-en-4-yl 2,2-dimethylbutanoate |  |
| BAJ 2510; BAJ 2740-enol<br><br>3-(2,4-dichlorophenyl)-4-hydroxy-1-oxaspiro[4.5]dec-3-en-2-one |  |
| BAJ 2740-ketohydroxy<br><br>3-(2,4-Dichlorophenyl)-3-hydroxy-1-oxaspiro[4.5]decane-2,4-dione |  |
| BAJ 2740-dihydroxy<br><br>3-(2,4-Dichlorophenyl)-3,4-dihydroxy-1-oxaspiro[4.5]decane-2-one |  |
| BAJ 2740-dioxoketone |  |
| 2,4-dichloromandelic acid hydroxycyclohexyl ester |  |
| 2,4-dichloromandelic acid |  |
| DCB-acid<br><br>2,4-Dichlorobenzene acetic acid; 2,4-Dichlorobenzoic acid |  |

## Attachment 2: Spirodiclofen Toxicity Profile.

**Acute Toxicity for Spirodiclofen.**

| OPPTS Guideline | Study Type | Results | Toxicity Category |
|---|---|---|---|
| 870.1100 | Acute oral toxicity / rat | $LD_{50}$ => 2000 mg/kg (males and females) | III |
| 870.1200 | Acute dermal toxicity / rat | $LD_{50}$ => 2000 mg/kg (males and females) | III |
| 870.1300 | Acute inhalation toxicity / rat | $LC_{50}$ => 5.03 mg/L (males and females) | IV |
| 870.2400 | Primary eye irritation / rabbit | Non-irritating | IV |
| 870.2500 | Primary dermal irritation / rabbit | Non-irritating | IV |
| 870.2600 | Dermal sensitization / guinea pig | Sensitizer | – |

**Subchronic, Chronic and Other Toxicity for Spirodiclofen.**

| Guideline No./ Study Type/ | MRID Nos. Doses/Classification | Results |
|---|---|---|
| 870.3100 Subchronic Oral - Rat | 45696715, 45696716 (1998,2003) (0,100,500,2500,12500 ppm) M:0,6.6,32.1,166.9,851.4 mg/kg/day F:0,8.1,47.1 215.3995.8 mg/kg/day Acceptable/guideline | For males, NOAEL = 32.1 mg/kg/day, LOAEL = 166.9 mg/kg/day based on increased incidence and severity of small cytoplasmic vacuolation in the cortex of adrenal glands, decreased cholesterol (week 5 and 13), and decreased triglycerides (week 5). For females, NOAEL= 8.1 mg/kg/day, LOAEL= 47.1 mg/kg/day based on increased incidence of small cytoplasmic vacuolation in the cortex of adrenal glands. |
| 870.3100 Subchronic Oral - Mouse | 45696711,45696712,45696713(1997) (0,100,1000,10,000 ppm) M:0,15,164,1640 mg/kg/day F: 0,30,234,2685 mg/kg/day Acceptable/guideline | For males, NOAEL= 15 mg/kg/day, LOAEL= 164 mg/kg/day based on an increased incidence of hypertrophic Leydig cells in the testes. For females, NOAEL = 30 mg/kg/day, LOAEL= 234mg/kg/day based on an increased incidence of cytoplasmic vacuolation of the adrenal cortex. |
| 870.3150 Subchronic Oral - Dog | 45696803,45696804 (2000) (0,200,630,2000 ppm) 0,7.7,26.6,84.7 mg/kg/day (M) 0,8.4,28.0,81.0 mg/kg/day(F) Acceptable/guideline | For males, NOAEL= 7.7 mg/kg/day, LOAEL = 26.6 mg/kg/day based on decreased body-weight gains, increased liver and adrenal weights, decreased prostate weights, and histopathology findings in the adrenal glands, testes, epididymis, thymus, and prostates. For females, NOAEL ≤8.4 mg/kg/day. LOAEL=8.4 mg/kg/day based on increased adrenal gland weight (two out of four animals) which coincided with histopathology findings (cytoplasmic vacuoles in the Zona fasciculata of the adrenal glands). |
| 870.3200 28-Day dermal toxicity - Rat | 45696806 (1999) 0, 1000 mg/kg/day Unacceptable/Guideline | The NOAEL=1000 mg/kg/day (HDT); however, the histopathology was not appropriately conducted as required by the guideline. The study did not examine all of the tissues, especially the possible target organs (i.e., uterus, prostate, etc). |
| 870.3700a Prenatal developmental - Rat | 45696906 (2000) 0,100,300,1000 mg/kg/day Acceptable/Guideline | Maternal: NOAEL =1000 mg/kg/day (HDT) Developmental:NOAEL= 300 mg/kg/day, LOAEL =1000 mg/kg/day based on an increased incidence of slight dilatation of the renal pelvis. |
| 870.3700b Prenatal developmental - Rabbit | 45696714 (1998) 0,100,300,1000 mg/kg/day Acceptable/guideline | Maternal: NOAEL = 100 mg/kg/day, LOAEL =300 mg/kg/day based on body-weight loss and decreased food consumption. Developmental: NOAEL =1000 mg/kg/day (HDT) |

| Subchronic, Chronic and Other Toxicity for Spirodiclofen. | | |
|---|---|---|
| Guideline No./ Study Type/ | MRID Nos. Doses/Classification | Results |
| 870.3800 Reproduction and fertility effects - Rat | 45696802,45696709 (2000) (0,70,350,1750 ppm) M: 0,5.2,26.2,134.8 mg/kg/day F: 0,5.5,27.6,139.2 mg/kg/day Acceptable/guideline | **Parental/system:** For males: NOAEL= 5.2-6.4 mg/kg/day, LOAEL =26.2-30.2 mg/kg/day based on decreased body weight in $F_0$ males; decreased absolute and relative liver weight in $F_0$ males; decreased cholesterol and triglycerides in $F_1$ males; and increased severity of adrenal cortical vacuolation in $F_1$ males. For females, NOAEL= 5.5-7.0 mg/kg/day, LOAEL= 27.6-34.4 mg/kg/day based on decreased unesterified fatty acids in $F_1$ females, and increased severity of adrenal cortical vacuolation in $F_0$ and $F_1$ females. **Reproductive**: For males: NOAEL= 26.2-30.2 mg/kg/day, LOAEL=134.8-177.6 mg/kg/day based on delayed sexual maturation; decreased testicular spermatid and epididymal sperm counts (oligospermia); and atrophy of the testes, epididymides, prostate and seminal vesicles. For females: NOAEL= 27.6-34.4 mg/kg/day, LOAEL= 139.2-192.7 mg/kg/day based on increased severity of ovarian luteal cell vacuolation/ degeneration. **Offspring**: NOAEL= 5.2-6.4 (M)/5.5-7.0 (F) mg/kg/day, LOAEL= 26.2-30.2 (M)/ 27.6-34.4(F) mg/kg/day based on decreased body weight and weight gain in $F_1$ male and female pups. |
| 870.4300 Chronic toxicity -Rat | 45696808,45696809 (2000) (0,50,100,350,2500 ppm) M: 0,2.0,4.1,14.7,110.1 mg/kg/day F: 0,2.9,5.9,19.9,152.9 mg/kg/day Acceptable/guideline | For males: NOAEL= 14.7 mg/kg/day, LOAEL= 110.1 mg/kg/day based on decreased body weights, decreased body-weight gain, increased APh levels, decreased cholesterol and triglyceride levels, increased vacuolated jejunum enterocytes, and increased incidences of Leydig cell hyperplasia. For females: NOAEL= 19.9 mg/kg/day, LOAEL= 152.9 mg/kg/day based on decreased body weights, decreased body-weight gain, increased APh levels, increased TSH, uterus nodules, and increased vacuolated jejunum enterocytes. **↑testes Leydig cell adenoma in males, ↑uterine adenoma and/or adenocarcinoma in females.** |
| 870.4100b Chronic toxicity - dog | 45696810,45696811 (2001) (0,20,50,150,500/600 ppm) M: 0,0.56,1.38,4.33,16.1 mg/kg/day F: 0,0.59,1.52,4.74,17.7 mg/kg/day Acceptable/guideline | NOAEL= 1.38 (M)/1.52(F) mg/kg/day, LOAEL= 4.33(M)/4.74 (F) mg/kg/day based on increased relative adrenal weights in both sexes, increased relative testis weight in males and histopathology findings in the adrenal gland of both sexes. |
| 870.4200b Carcinogenicity - mouse | 45696724 (2000) (0,25,3500,7000 ppm) M: 0,4.1,610,1216 mg/kg/day F: 0,5.1,722,1495 mg/kg/day Acceptable/guideline | NOAEL= 4.1(M)/5.1(F) mg/kg/day, LOAEL= 610 (M) mg/kg/day based on increased absolute and relative liver and adrenal weights, decreased absolute and relative kidney weight, enlarged adrenal gland, discolored testis, adrenal gland vacuolization, interstitial cell degeneration of the testes. For females, LOAEL= 722 mg/kg/day based on increased absolute and relative adrenal weight, decreased absolute and relative kidney weight, increased incidences of adrenal gland pigmentation, and adrenal vacuolization. **↑Hepatocellular adenoma and carcinoma.** |
| 870.5100 Gene mutation Salmonella typhimurium | 45696702 Acceptable/guideline | There was no evidence of increased revertant colonies above control in 5 Salmonella strains (TA1535, TA1537, TA1538, TA100, TA98) ± S9 at concentrations up to 5000 µg/plate. |

| Subchronic, Chronic and Other Toxicity for Spirodiclofen. | | |
|---|---|---|
| Guideline No./ Study Type/ | MRID Nos. Doses/Classification | Results |
| 870.5300 In vitro Mammalian Cell Gene Mutation | 45696614 Acceptable/guideline | Negative, tested in Chinese Hamster lung fibroblast V79 cells at concentrations up to 300 ug/mL -S9 and +S9. Cytotoxicity was observed at ≥15 ug/mL -S9 and 80 ug/mL +S9. |
| 870.5375 In vitro Mammalian Chromosome Aberration | 45696615 (1996) Acceptable/guideline | Negative, tested in Chinese hamster lung (V79) cells at concentrations 5-80 ug/mL or 0.75-12 ug/mL -S9 or 10-160 ug/mL +S9. |
| 870.5395 In vivo Mouse Bone Morrow Micronucleus | 45696701 (1996) Acceptable/guideline | Negative, tested at a dose 800 mg/kg (MTD). Clinical signs and cytotoxicity were seen at 800 mg/kg. |
| 870.6200 Acute Neurotoxicity - Rat | 45696725 (2000) 0,200,500,2000 mg/kg Acceptable/guideline | NOAEL = 2000 mg/kg/day, no neurotoxicity observed. |
| 870.6200 Subchronic neurotoxicity - Rat | 45696726 (2001) (0,100,1000,12500 ppm) M: 0,7.2,70.3,1088.8 mg/kg/day F: 0,9.1,87.3,1306.5 mg/kg/day Acceptable/guideline | NOAEL= 70.3(M)/87.3(F) mg/kg/day. LOAEL= 1088.8(M)/ 1306.5(F) mg/kg/day based on decreased body weights, food consumption, and increased urine staining in both sexes and decreased motor and locomotor activity (week 4) in females only. |
| 870.6300 Developmental neurotoxicity | 46324901 (2004) (0, 70, 350 or 1500 ppm) 0/0, 6.5/14.0, 32.1/69.7 or 135.9/273.8 mg/kg/day (gestation/lactation) The study classification is reserved for the guideline requirement pending receipt of additional morphometric measurements for the low and mid dose groups. | Maternal NOAEL = 135.9/273.8 mg/kg/day LOAEL = Not established. Offspring NOAEL = Not established LOAEL = 6.5/14.0 mg/kg/day based on effects in memory phase of the water maze test in PND 60 females. |
| 870.6300 Developmental neurotoxicity | 47166501 (2007) (0, 70, 350 or 1500 ppm) 0/0, 5.4/13.0, 28.6/65.7 and 119.2/262.1 mg/kg/day (gestation/lactation) | Maternal NOAEL=119.2/262.1 mg/kg/day LOAEL= Not established Offspring NOAEL = 119.2/262.1 mg/kg/day LOAEL= Not established |

## Attachment 3: Summary of Toxicological Doses and Endpoints.

| **Summary of Toxicological Doses and Endpoints.** | | | |
|---|---|---|---|
| Exposure Scenario | Dose Used in Risk Assessment, UF | FQPA SF and Level of Concern for Risk Assessment | Study and Toxicological Effects |
| Acute Dietary | An appropriate endpoint attributable to a single dose was not identified. Assessment not necessary. | | |
| Chronic Dietary (All populations) | NOAEL= 1.38 mg/kg/day<br>UF = 100<br>cRfD = 0.014 mg/kg/day | FQPA SF = 1x<br>cPAD = cRfD ÷ FQPA SF = 0.014 mg/kg/day | Chronic Oral Toxicity Study in Dogs; LOAEL= 4.7 mg/kg/day based on increased relative adrenal weights in both sexes, increased relative testis weight in males and histopathology findings in the adrenal gland of both sexes. |
| Short-term Incidental Oral, Dermal and Inhalation (1-30 Days) | LOAEL = 8.4 mg/kg/day<br>dermal-absorption rate= 2% | FQPA SF = 3x<br>Residential/Occupational LOC for MOE <300 | Subchronic Oral Toxicity Study in Dogs; LOAEL= 8.4 mg/kg/day based on increased adrenal gland weight (two out of four animals) which corroborated with histopathology findings (cytoplasmic vacuoles in the Zona fasciculata of the adrenal glands) in females; a NOAEL for females was not established. |
| Intermediate-term Incidental Oral, Dermal, and Inhalation (1-6 Months) | NOAEL = 1.38 mg/kg/day<br>dermal-absorption rate = 2% | FQPA SF = 1x<br>Residential/Occupational LOC for MOE <100 | Chronic Oral Toxicity Study in Dogs; See above under Chronic Dietary. |
| Long-term Dermal and Inhalation (>6 Months) | NOAEL = 1.38 mg/kg/day<br>dermal-absorption rate = 2% | FQPA SF = 1x<br>Residential/Occupational LOC for MOE <100 | Chronic Oral Toxicity Study in Dogs; See above under Chronic Dietary. |
| Cancer; Oral, Dermal, and Inhalation | Classification: "Likely to be Carcinogenic to Humans"; $Q_1^*$ $(mg/kg/day)^{-1} = 1.49 \times 10^{-2}$. | | |

UF = uncertainty factor. RfD = reference dose. LOC = level of concern. MOE = margin of exposure = NOAEL ÷ exposure.